REMARKS

Applicants herein traverse and respectfully request reconsideration of the rejection of the claims 1-5 as cited in the above referenced Office Action in view of the remarks set forth below.

I. The Rejection of Claims 1-5 Under 35 U.S.C. §101, 112, first Paragraph May Properly Be Withdrawn:

The Examiner contends that the prohibitions of 35 U.S.C. §101 dictate rejection of claims 1-5 for the reasons set forth in the outstanding Office Action. Reconsideration of the rejection of the above claims under 35 U.S.C. §101 and §112, First Paragraph is respectfully requested.

Specifically, the Office rejects the above claims under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for lack of utility. In particular, the Office questions whether applicants provide a specific and substantial asserted utility, or a well established utility.

The Examiner contends that the claimed invention is "not supported by either a specific and substantial asserted utility or a well established utility." In a nutshell, the Examiner's position can best be summarized as noting that since HG52's ligand is not known, the receptor's function has yet to be established and a well established utility is lacking. The rejection continues that Applicants' assertion that HG52 may be used to identify modulators of HG52 mediated disorders asserts only a general activity since further experimentation is required to confirm a "real world" context of its use. The rejection continues that the disclosed use for the nucleic acid molecule of the present invention is generally applicable to any nucleic acid and thus is not particular to the nucleic acid sequence claimed. Based on the above, the Examiner concludes the invention is not in available form. Applicants respectfully traverse.

> According to the Office Action,
>
> The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a specific and substantial utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.
>
> Office Action page 3.

The examiner further opines that while the novel polypeptide, HG52 has been "assigned a function because of its similarity to known proteins (Specification at 18, line 11)," he

maintains that such assignment of function based upon sequence similarity is prone to error, referring to Doerks et al. (1998) as support for this assertion.

In order to satisfy the statutory utility requirement, a patent application must either explicitly or implicitly establish that the claimed invention is useful for some purpose. In practice, the provisions of the current Utility Examination Guidelines (66. Fed. Reg. 1092, January 5, 2001) (referred to herein as "The Guidelines") require the application set forth a specific, substantial and credible utility for the invention at the time the application is filed.

The Guidelines establish that evidence of a well-established or an asserted utility can be derived from utilities taught in the closest prior art.

Applicants maintain that the legal standard that must be followed in order to make such a rejection is well-established and clearly set out in the Manual of Patent Examining Procedure:

"Where the asserted specific and substantial utility is not credible, a *prima facie* showing of no specific and substantial credible utility must establish that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention." MPEP (8th edition) 210711 (C)(2).

Generally speaking, an invention has a "well-established" utility:

1. if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and

2. The utility is specific, substantial and credible (66 Fed. Reg. 1092, 1098).

Applicants maintain that the instant disclosure indicates that the claimed subject matter has a well-established utility that a skilled artisan would immediately recognize as a specific, substantial and credible utility. This position is based on the observation that the teachings of the art of record clearly supports a finding that there was an art-recognized, well-established utility for thrombin-like receptors, exemplified by the disclosed polypeptide designated HG52. This position is based, in part, on the fact that publications reporting cDNA and genomic DNA cloning of human thrombin receptor homologues, thrombin receptors including PAR- proteinase activated receptors like PAR-1, -2 and -3 were available prior to the filing date of the instant disclosure and that the art appreciated both the existence of receptors that are selective for thrombin and the fact that thrombin receptors and homologues thereof have therapeutic utility because of their potential role in a regulatory thrombin and other ligands that bind the thrombin receptor and mediate the thrombin mediated signaling pathway. As well, Applicants note that various thrombin receptor antagonists are currently in use.

The 2001 Guidelines indicate that if it is apparent that the claimed invention has a well-established utility, an Examiner should not enter a rejection for lack of utility, even if the

applicant has made no specific assertion of utility. Accordingly, based on the reasoning provided herein, Applicants respectfully propose that the rejection for lack of utility under Section 101 and under the first paragraph of Section 112, should be withdrawn.

The invention at issue is drawn to polypeptide sequence corresponding to a gene that is expressed in humans as a transcript of about "4.5 kb, especially in cells of the immune system (peripheral lymphocytes (PBLs), spleen, bone marrow, lymph nodes). Page 5, lines 30-34. The specification notes further that HG52 "most likely represents a novel G-protein coupled receptor (GPCR) of the rhodopsin family" based, *inter alia*, upon its structural features, e.g., seven membrane domain; homology with members of the rhodopsin family and signature motifs of GPCRs in the rhodopsin family. See page 5, lines 23-29. Also see page 18, line 11. While the Examiner concedes that the application assigns function to the disclosed polypeptides based upon sequence similarity, he however, favors the interpretation that sequence-to-function methods of assigning protein function are erroneous. He supports this conclusion based upon Doerks et al. (1998).

At the outset, Applicants note that traditional ligand-binding approaches to identify a functional thrombin receptor have succeeded in identifying a number of thrombin-binding proteins (Gronke et al., 1987; Okamura et al., 1978)Doerks et al. report on predicting protein function. It is important to note that the reference is not drawn to "orphan receptors" per se but instead to "putative, poorly annotated proteins that are usually labeled as "hypothetical" or just as "ORF." Thus, unlike GPCRs which are well characterized, the proteins used in Doerks et al. were "poorly annotated" from the start. Thus, it is not seen how the instructions contained in Doerks et al. can be imputed to GPCRs in general, and GPCRs of the rhodopsin family of GPCRs in particular, and more particularly to the thrombin receptor, of which, Applicants maintain the HG52 is most closely related to.

Applicants note further that the Doerks et al. reference, on which the Examiner places significant reliance, is innocently silent with respect to the degree of homology between two proteins under investigation. Likewise, there is no discussion in this reference about what impact percent degree of amino acid sequence identity between two proteins would have in assigning protein function. Conceivably, a protein having only 10% amino acid sequence identity may differ from one having about 30% identity. Indeed, in the absence of teaching about percent (%) homology, one of skill in the art reading the reference would not necessarily conclude as did the examiner that assigning function based upon sequence similarity is *a priori* error prone.

Of equal import is the instructions on page 250 of the Doerks et al. reference, penultimate paragraph, wherein Doerks et al. note that "We were able to provide some functional annotation for more than 700 of about 1300 proteins clustered in 25 of the 58 distinct UPFs."

Page 250, penultimate paragraph. Thus, in more than 50% of the proteins studied by Doerks et al., they were able to assign some function based principally on sequence similarity.

The instructions continues that:

> Most of them are currently named "hypothetical protein" so that their annotation adds enormous value to their sequences. For another 13 UPF's currently containing about 250 proteins, the presence of transmembrane regions was recorded. This annotation is now being recorded into PROSITE and SWISS-PROT so that these features can be assigned to newly sequenced genes as well."

Thus, it would appear that Doerks et al. place significant reliance on sequence identity as a means of assigning functions to a particular protein. Consequently, Applicants maintain that a skilled artisan reviewing the Doerks et al. reference would necessarily conclude that protein function may be based upon percent (%) amino acid sequence identity.

In further support of the above, i.e., that percent amino acid sequence identity is predicative of function, Applicants propose that it is well-established and accepted by the scientific community that a particular degree of percentage identity over a particular length of a protein is sufficient to establish a likelihood of homology and shared functionality. Applicants aver that percentage similarity with a protein of known function can be used as a reliable and scientifically valid predictor of function.

In support of their position that sequence similarity is predictive of function , Applicants specifically draw the Examiner's attention to the attached paper (Exhibit 2) by Steven Brenner *et al. (1998) Proc. Natl. Acad. Sci. USA 95:6073-6078.* Therein the authors, through exhaustive analysis of a dataset of proteins with known structural and functional relationships, determined that *30%* identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least *150* residues, and that 40% identity is a reliable threshold when aligned over at least *70* residues (pages *6073* and *6076).* Applicants maintain that, in view of Brenner et al. and contrary to the Examiner's position, a sequence identity of about 28.3% over a length of 359 amino acids is sufficient to assign a function to a protein, especially considering the overall length of the protein.

It is Applicants position that one skilled in the art after a careful reading of Brenner *et al.* will necessarily conclude as did the authors that sequence-to-function methods of assignment are very reliable. In the attached paper, the authors analyzed many individual pairs of proteins (taken from two compiled databases, both from the Protein Data Base, "PDB"), which proteins were known to be unrelated to each other (through non-sequencing analysis). The authors, essentially posed the query "What is the probability that these two unrelated proteins will show a certain percentage identity to each other over a certain length?" i.e., 50%

identity over 150 residues. In this way, *Brenner et al.* evaluated the reliability of using sequence comparison methods to determine the evolutionary and functional relationships between pairs of proteins. In order to conduct an analysis that was not wholly tautologous (i.e. because the degree of relatedness had been previously determined by sequence comparisons), the authors needed to select proteins whose structure and function were already well defined, and had been determined by methods other than sequence comparison. That is why the authors used the PDB, a database with over 12,000 molecules with structures and functions identified by methods other than sequence comparison.

As a result of their analysis, the authors, Brenner *et al.*, produced a graph (Fig. 3) that clearly shows the probability of two unrelated proteins sharing a certain degree of sequence identity over a certain length. Based upon the date presented, one of skill in the art would not expect the results reported in the Brenner *et al.* paper to be specific to the data analyzed in that paper, but would expect them to be generally applicable to proteins compared using standard sequence comparison methods (Brenner et al., 6074, col. 2, last sentence of para. 4).

Of equal importance is the observation by Brenner et al. regarding pair-wise sequence comparison methods such as BLAST that "Because many homologs have low sequence similarity, most distant relationships cannot be detected by any pair-wise comparison method; however *those which are identified may be used with confidence*. (Emphasis added.).

As reported in the accompanying sequence alignment (Exhibit 2) the amino acid sequence of SEQ ID NO:2 shares significant sequence identity with known thrombin receptors. Specifically, the amino acid sequence of HGF52 (359 amino acids) is aligned with the amino acid sequences of three thrombin receptors- PAR-1, -2 and -3. The data make clear that HG52 has a sequence similarity of from 22 to 28.3% with the thrombin receptors and particularly with PAR1L it shares a sequence similarity of about 29% (28.3%). Applicants respectfully submit that the degree of identity between HG52 of 359 amino acids and known thrombin receptors, would be sufficient to lead a person skilled in the art to believe that it is more likely than not that any specific and substantial utility asserted by the applicant is credible.

Applicants maintain that as noted in the specification that the polypeptide of SEQ ID NO:2 is a member of a well-known and important family of GPCRs. See page 5 of the specification. In general, GPCRs represent the primary mechanism by which cells sense alterations in their external environment and convey that information to the cells' interior. The binding of an agonist to the receptor promotes conformational changes in the cytoplasmic domains that lead to the interaction of the receptor with its cognate G protein(s). Agonist-promoted coupling between receptors and G proteins leads to the activation of intracellular effectors that substantially amplify the production of second messengers feeding into the signaling cascade. Effectors are more often (i) enzymes e.g. adenylate cyclase, which converts

ATP to cAMP, or phospholipase C, which hydrolyses inositol lipids in membranes to release inositol trisphosphate, which in turn mobilizes Ca^{2+} within a cell or (ii) ion channels, many second messenger molecules can be produced as the result of a single agonist binding event with its receptor. In turn, changes in the intracellular levels of ions or cAMP, or both, result in the modulation of distinct phosphorylation cascades, extending through the cytosol to the nucleus, that eventually culminate in the physiological response of the cell to the extracellular stimulus. It is well accepted that the overall paradigm noted supra is apparently the same for all GPCRs.

To date, more than 800 GPCRs have actually been cloned from a variety of eukaryotic species, from fungi to humans. See L. F. Kolakowski in GCRDb-WWW The G Protein-Coupled Receptor DataBase World-Wide-Web Site (http://receptor.mgh.harvard.edu/GCRDBHOME. html.org)].

Functionally, GPCRs share in common the property that upon agonist binding they transmit signals across the plasma membrane through an interaction with heterotrimeric G proteins. For example, Stadel et al., Trends Pharmacol. Sci., 18:430-437 (1997) note that GPCRs respond to a vast range of agents including proteases such as **thrombin**, which activates its receptor by cleaving off a portion of the amino terminus.

Applicants respectfully submit that one of ordinary skill in the art armed with the teachings of the references cited herein taken together with the alignment data appended hereto would reasonably expect that the polypeptide of the invention (HG52) would, more likely than not, possess the function of a thrombin receptor, e.g., PAR-1L. As such, it is Applicants' position that the novel protein may be used to identify modulators of the thrombin receptor family as well as used in various screening assays to identify additional modulators of the thrombin receptor and be used to identify dysfunctional thrombin mediated disorders.

Applicants note further that GPCRs receptors are known to be instrumental in regulating a plethora of responses in the human body including, but not limited to an immune response, and therefore are very important in medical research. Consequently, identifying new GPCRs and determining their roles and interactions in regulating immune response provides an immediate benefit to the public by 1) providing potential new drug targets, 2) by providing additional important proteins for use in differential expression and toxicology assays, and 3) by expanding the body of medical knowledge in the field of regulating immune response. HG52 is one such molecule. And even if a composition's *only* use is for fundamental scientific research, this is still a legitimate and patentable use. (See discussion of relevant utility issues, above, especially MPEP 2107 (I) and *Nelson v. Bowler, 206 USPQ 881*).

In further support of the rejection under sections 101 and 112, first paragraph, the Examiner on page 4 of the Office Action opines that

> "Even, if arguendo, the nucleic acid encoding the HG52 protein is found to be a G-protein coupled receptor, it is an orphan receptor." The Examiners position can be best summarized as hypothesizing that since the ligand to the disclosed protein is unknown, e.g., the protein has not been de-orphanized, the function is thus unknown and "neither the specification nor the art of record discloses any diseases or conditions associated with the function or expression of the HG52 protein, therefore, there is no "real world" context of use. The Examiner continues that because of the lack of a ligand, efforts at identifying a ligand will necessarily involve "undue experimentation" and as such the protein lacks a "real world use".

Applicants respectfully disagree with the above conclusion for reasons that follow.

Attached as Exhibit 3 is a Review[1] entitled "**Orphan G protein-coupled receptors: a neglected opportunity for pioneer drug discovery**", Jeffrey M. Stadel, Shelagh Wilson and Derk J. Bergsma, Trends Pharmacol. Sci., 18:430-437 (1997), ("Stadel et al.") which contrary to the Examiner's position, makes clear that as early as 1997, it was routine to identify ligands for "orphan receptors" based upon sequence similarity. The reference makes clear that, as early as 1997, it did not constitute undue experimentation to identify a ligand for an "orphan receptor" especially when using the proposed "Reverse Molecular Pharmacological Strategy" ("RMP") proposed therein and (ii) sequence similarity between sequences is sufficient to assign a function to the unknown orphan receptor. This position is amply supported by the various examples disclosed in the reference.

To date, the novel technologies developed in association with genomic research have had a significant impact on the way investigations into the basis of disease are being conducted and according to Stadel et al. will, greatly enhance the means by which diseases will be diagnosed and treated in the future. Stadel et al. proposes that in order to keep pace with the evolution of molecular medicine, the pharmaceutical industry must take great strides in embracing new technologies to identify novel targets for drug discovery. The major question, according to Stadel et al. that remains to be addressed concerns how to convert genomic sequences into therapeutic targets in an expeditious manner and eventually to obtain pharmaceutical drugs that will enhance the quality of life. One such strategy proposed by Stadel et al. is referred to a "Reverse Molecular Pharmacology" which according to Stadel et al. will aid in the identification of ligands for "orphan receptors" without the exercise of "undue experimentation".

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[1] This reference was previously submitted in an IDS dated June 16, 2003.

According to Stadel et al., about 140 human GPCRs have been cloned for which the cognate ligands are also known. As well, more than 100 orphan GPCR family members have been identified via traditional molecular genetic approaches.

With respect to the "orphan receptors", the reference notes that

> "By definition, there is enough sequence information in the receptor cDNAs to place them clearly in the superfamily of GPCRs, but often there is insufficient sequence homology with known members of this family to be able to assign their ligands with confidence or predict their function.

The instruction continues that

> . . . there are currently over 240 human GPCRs, excluding sensory receptors. As the size of sequence databases continues to increase, this list is expected to grow to 400, and perhaps even to 1000 or more unique gene products. The list will grow even further as paralogues and alternatively spliced GPCR variants emerge. Most orphan GPCRs share a low degree of sequence homology (typically about **25–35%** overall amino acid sequence identity), with known GPCRs, suggesting that they belong to new subgroups of receptors. . . . Nevertheless, the majority of orphan receptors are phylogenetically distributed among a broad spectrum of distantly related, known receptor subgroups. (Emphasis supplied)

Interestingly, Stadel et al. pose the question "What is the rationale for investing considerable time and resources into trying to establish the function of orphan GPCRs?"

Applicants note as did Stadel et al. that since GPCRs have a proven history of being excellent therapeutic targets, and further considering that within the past two decades, several new drugs have been registered that are directed towards activating or antagonizing GPCRs; most research efforts in the pharmaceutical industry are and should be focused on this signaling pathway mediated by GPCRs.

The current paradigm for identifying GPCRs as drug discovery targets relies upon the functional activity. That is to say that according to this traditional strategy the starting point is functional activity, which forms the basis of an assay by which a ligand is identified generally through purification from biological fluids, cell supernatants or tissue extracts. Upon its isolation, the ligand is used to characterize its cellular and tissue biology as well as its pathophysiological role. Subsequently, cDNAs encoding corresponding receptors are 'fished' from gene libraries using a variety of methodologies (e.g. receptor purification and expression cloning) that often either directly or indirectly use the ligand as the 'hook'. As the nucleotide sequences for GPCRs begin to accumulate and be analyzed, additional receptors can be cloned by homology screening, by positional cloning, and by polymerase chain reaction (PCR) methodologies that use oligonucleotide primers based on nucleotide sequences conserved within

the seven transmembrane domains of the GPCR family. Upon expression of the cloned human receptor cDNA in a heterologous cell system, it is used, together with its ligand, to form the basis of a screen to explore chemical compound libraries for receptor antagonists or agonists. Lead structures identified via this iterative process are further refined through medicinal chemistry using an iterative process. Thereafter, resulting drug leads with appropriate in vivo pharmacology are passed on into the clinic for development. The identification of vasoconstricting peptide endothelin is one such example.

A drawback attending the traditional approach, according to Stadel et al. is that the traditional approach may not work for "orphan receptors". Consequently, the traditional approach ignores a plethora of potential drug target. To address this problem, Stadel et al. detail a recent shift in the current paradigm to the introduction of a new reverse molecular pharmacological strategy. Stadel et al. argue that a consequence of the recent advances in molecular and recombinant biology, e.g., molecular cloning techniques and, more recently, mass sequencing of expressed sequence tags (ESTs) from cDNA libraries, has made it possible for a skilled artisan to identify GPCRs through computational or bioinformatic methodologies. For example, the EST approach, proposes

(i) sequencing cDNAs randomly picked from a collection of cDNA libraries;

(ii) followed by extensive bioinformatic analysis of the sequence to identify structural signatures characteristic of GPCRs;

(iii) upon identifying new members of a GPCR superfamily, the recombinantly expressed receptors are used in functional assays to search for the associated novel ligands; and

(iv) the receptor-ligand pair are thereafter used for compound bank screening to identify a lead compound that, together with the activating ligand, is used for biological and pathophysiological studies to determine the function and potential therapeutic value of a receptor antagonist (or agonist) in ameliorating a disease process.

Stadel et al. further propose that clues as to therapeutic potential may involve receptor genotyping of disease populations. Once a link with a disease is finally identified, an appropriate compound can be advanced for clinical study.

That the rewards far outweigh the effort is evident from the observation by Stadel et al. that ". . . the potential reward of using this approach [the reverse molecular pharmacological strategy-RMP] is that resultant drugs naturally will be pioneer or innovative discoveries, and a significant proportion of these unique drugs may be useful to treat diseases for which existing therapies are lacking or insufficient."

That the strategy is workable is evident from the examples that are beginning to emerge from several efforts showing that progress has been made in characterizing orphan GPCRs.

As a first example, Stadel et al. detail the identification of an orphan GPCR that functions as a calcitonin gene-related peptide (CGRP) receptor. CGRP is a peptide of 37 amino acids, widely distributed in neurones, and functions as a potent vasodilator. It was postulated to be involved in migraine and had also been implicated in non-insulin-dependent diabetes mellitus because it promotes resistance to insulin. Using the proposed RMP strategy, an orphan GPCR EST was derived from a human synovium cDNA library, which showed substantial sequence similarity to the human calcitonin receptor and was hence originally expected to be a new subtype of the calcitonin receptor. The message for this novel receptor was expressed predominantly in lung, which is known to be a relatively rich source of CGRP receptors. Following the full-length cloning from a human lung library, the orphan receptor cDNA was stably expressed in HEK293 cells. Both radioligand binding using ^{125}[I]CGRP, as well as functional assays of CGRP-stimulated cAMP accumulation, demonstrated an appropriate pharmacological profile for the expressed receptor **similar** to that observed with endogenous CGRP receptors on human neuroblastoma cells.

The instruction continues that in addition to identifying the CGRP receptor, the reverse molecular pharmacology approach has also been successful in identifying other orphan receptors, such as the anaphylatoxin C3a receptor.

The above examples represent receptors with significant homology to known GPCR superfamily members where their activating ligands proved to be known GPCR ligands.

Other examples detailing "ligand fishing" as a means for identifying novel endogenous ligands are also detailed herein. In furtherance of this objective, Stadel et al. detail the work two groups that investigated an orphan opioid-like receptor, ORL1 – Refer to Reference # 47 and 48 of Exhibit 3.

According to the reference, both groups expressed the orphan GPCR in CHO cells and challenged the transfected cells with a series of opiate agonists, but without response. Both groups then used a similar ligand fishing approach as outlined in the review. Taking crude extracts from rat brain or porcine brain, each group screened against the stably transfected cell lines using inhibition of adenylate cyclase activity as a functional assay. The group was able to fractionate the brain extracts and identify the novel dynorphin-like ligand, which they called nociceptin (Ref. 47) or orphanin FQ (Ref. 48). Based upon the data presented, each group successfully established a functional assay in transfected CHO cells that allowed the purification of a novel neuropeptide ligand that was 17 amino acids long for the orphan receptor. This work, according to Stadel et al. validates the ligand fishing approach for characterizing the function of orphan GPCRs.

Stadel et al. conclude that

"Because of the proven link of GPCRs to a wide variety of diseases and the historical success of drugs that target GPCRs, we believe that these orphan receptors are among the best targets of the genomic era to advance into the drug discovery process."

In view of the above recitation, one skilled in the art of molecular biology would necessarily conclude that "orphan receptors" not only have utility in drug discovery but also that a skilled artisan using conventional molecular biology techniques, e.g., the Reverse Molecular Pharmacological Strategy proposed by Stadel et al. will be able to identify ligands for orphan receptors without the exercise of "undue experimentation" as well as assigning function based upon sequence homology.

At page 5 of the pending Office Action, the Examiner cites *Brenner v. Manson* , 148 USPQ 689 (Sup. Ct. 1966) to support his position that "further characterization" of the disclosed polypeptide amounts to merely a further act of the invention and in the absence of "either immediately obvious or fully disclosed "real world" utility the claimed invention is incomplete.

The Examiner's position can best be summarized as follows;

"Until some actual specific significance can be attributed to the protein identified in the specification as HG52, the instant invention is incomplete. . . . In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediate obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which inhibit its activity is clearly to use it as an object of further research which has been determined by the courts to be non-patentable."

The Examiner characterizes the Court in Brenner stating that despite a steroid having similarity with adjacent homologues, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics (page 6, lines 4-6 of the Office Action).

Applicants respectfully suggest that the Examine has misread and/or misapplied the case. The invention in Brenner was not a compound as is the case in the instant application-polypeptides and cDNA encoding said polypeptides. The invention claimed was a chemical process that produced steroids. The question presented to the Supreme Court was whether a chemical process was "useful" if it produced a compound belonging to a useful class (p 695 in Brenner v. Manson 148 USPQ 689 (1966)). In footnote 19, the Court stated that minor changes in the structure of a steroid may produce profound changes in its biological activity. Therefore, in Brenner, there was a substantial likelihood that a steroid produced by the claimed process may be a useless member of that class. This is clearly not the situation in the present case. Applicants are claiming compounds, not a chemical process, and the Examiner has not stated that

the GPCRs to which the claimed compounds belong contain a substantial number of useless members. In addition, the class of GPCRs (thrombin receptors) that the compounds of the invention most closely resemble, itself has utility, - thrombin receptor antagonists useful for modulating thrombin mediated disorders, a class of compounds having an obvious and well known utility. As a consequence, since the family of GPCRs is known to contain a substantial number of useful members, and the claimed compounds belong to this class, based, in part, upon sequence identify, there is sufficient likelihood that the claimed invention is useful and a rejection under 35 U.S.C. §101 is improper.

As well, the Examiner did not cite support in the MPEP for the use of the standard enunciated above. The applicants were not able to find support for the standard used by the Examiner either in the MPEP or in case law. The applicants have provided the publication by Brenner *et al.* and *Stadel et al.* that supports Applicants' position. If the Office wishes to maintain the rejection based on the above standard, the applicants request that evidence be provided that supports the position of the Office in the form of a Declaration pursuant to 37 C.F.R. 1.104(d)(2).

Accordingly, Applicants respectfully propose that based upon the various structural and functional features attending the polypeptides of the invention and those attending the rhodopsin family of GPCRs, and particular based upon the sequence identify between the thrombin receptors and the HG52 receptor, the novel HG52 most closely resembles the thrombin receptors.

For example, the claimed molecules are useful both for fundamental medical research purposes, and for the highly economically important and practical industrial purpose of providing target molecules for toxicological screening of potential drugs. At the time of filing it would have been clear to one of ordinary skill to use the claimed polypeptides to investigate the mechanisms of, for example, immunoregulatory function, platelet aggregation etc.

Other proposed utilities of the recombinant Thrombin Like Receptor (HG52) will become apparent from the discussion appearing hereunder.

Diagnostic and Screening Tool

The thrombin receptor is a G-protein coupled seven transmembrane receptor (T7G) which is present on platelets, endothelial cells, fibroblasts, mesangial cells, neural cells and smooth muscle cells. This receptor is activated by the irreversible cleavage of the extracellular, amino terminal sequence between arg.sup.41 and ser.sup.42 by thrombin or another serine protease thereby exposing a new N-terminus, referred to as the "neo-N-terminus". (Watson S and Arkinstall S (1994) The G-Protein Linked Receptor Facts Book, Academic Press, San Diego, Calif. pages 20-31.) The neo-N-terminus peptide (abbreviated P14) serves as a

tethered ligand that is capable of activating the receptor. The cleaved peptide fragment is detectable in biological fluids and can be used as a marker for thrombin receptor activation on platelets and other vascular cells. The activated receptor in turn, interacts with an intracellular G-protein complex which mediates further intracellular signalling activities such as the production of second messengers such as cyclic AMP (cAMP), phospholipase C, inositol triphosphate or ion channel proteins. Importantly, thrombin is known to activate more than one receptor.

Thrombin is a potent agonist for a number of biological responses that may mediate inflammatory and reparative responses to vascular injury (reviewed in Shuman, 1986). Thrombin aids in the formation of blood clots by catalyzing the conversion of fibrinogen to fibrin, which is an integral part of most clots. Thrombin-induced platelet activation is particularly important for arterial thrombus formation, a process that causes myocardial infarction and some forms of unstable angina and stroke. As an activator of both fibrin clot formation and platelet plug formation, thrombin plays a central role in hemostasis, thrombosis and atherosclerosis. Stimulation of platelets by thrombin causes phosphoinositide hydrolysis and mobilization of intracellular Ca^{2+} (Rittenhouse-Simmons, 1979), signaling events thought to be critical in platelet activation. Although the above events have been studied for many years, it is only within the past few years that the mechanism by which thrombin activates platelets and other vascular cells has been determined.

Consequently, the availability of the recombinant DNA encoding a thrombin like receptor, e.g., HG52 will permit expression of the receptor on host cell surfaces, thus making the cells available as a tool for evaluating the ability of candidate agonists or antagonists to bind to the thrombin receptor.

In a representative assay, competition of a candidate antagonist for binding to the HG52 receptor with either labeled thrombin, a thrombin agonist or known binding antagonist can be tested. The labeled substance known to bind the receptor can, for example, be P14. Varying concentrations of the candidate may be supplied along with a constant concentration of labeled thrombin, thrombin agonist, or antagonist, and the inhibition of a binding of label to the receptor can be evaluated using known techniques.

Assay systems for the effect of thrombin on recombinant cells expressing the HG52 receptor may include calcium mobilization and voltage clamp, all of which are well known to a skilled artisan. Other suitable endpoints include thrombin-induced phosphoinositol turnover and modulation, inhibition and/or activation of adenyl cyclase. These assays permit an assessment of the effect of the candidate antagonist on the HG52 receptor activity rather than simply ability to bind to thrombin.

As well, the available polypeptide of the invention – HG52 receptor proteins may be used as counter screens for compounds. For use in a counter screen, a skilled artisan need not know the ligand/agonist for said receptor considering that expression of the HG52 receptor is sufficient to generate a signal due to basal activity of the receptor. The basal activity/ reading, in turn, may be used to identify a class of antagonists, i.e., inverse agonists. As well, the HG52 receptor protein may be used to counter screen compounds that are known antagonists of the thrombin receptor or a related receptor.

Just as thrombin receptor antagonists peptides have been identified based on structure-activity studies involving substitutions of amino acids on thrombin receptors, similar studies may be carried out on the novel thrombin-like receptor HG52 to identify additional and more potent antagonist peptides effective at antagonizing thrombin receptors.

See Bematowicz et al, J. Med. Chem., 39 (1996), p. 4879-4887, which discloses tetra- and pentapeptides as being potent thrombin receptor antagonists, for example N-trans-cinnamoyl-p-fluoroPhe-p-guanidinoPhe-Leu-Arg-NH_2 and N-trans-cinnamoyl-p-fluoroPhe-p-guanidinoPhe-Leu-Arg-Arg-NH_2. Peptide thrombin receptor antagonists are also disclosed in WO 94/03479, published Feb. 17, 1994.

Polynucleotides of the present invention may be used as diagnostic reagents, through detecting mutations in the associated gene or a gene such as that encoding thrombin. Detection of a mutated form of thrombin receptor gene in the cDNA or genomic sequence and which is associated with a dysfunction will provide a diagnostic tool that can add to, or define, a diagnosis of a disease, or susceptibility to a disease, which results from under-expression, over-expression or altered spatial or temporal expression of the thrombin receptor gene. Individuals carrying mutations in the gene may be detected at the DNA level by a variety of techniques well known in the art.

Alternatively, the availability of the recombinant HG52 receptor protein will permit production of antibodies which may be made immunospecific to the activated form of the thrombin receptor which can then be used for diagnostic imaging of activated receptors *in vivo*. When injected in vivo, these antibodies will more likely home to the sites of the activated thrombin receptor, thus permitting localization of problem areas which are subject to thrombosis.

In conclusion, it is Applicants' position that one skilled in the art armed with the teachings in each of Brenner et al. and Stadel et al. together with the recitations noted above would necessarily conclude as do the Applicants that the novel polypeptide(s) of the invention are indeed useful in identifying modulators of the thrombin receptor. Consequently, Applicants assert that it is more likely than not that a person skilled in the art would consider credible the assertions noted here above that the polypeptide of the invention (HG52) would, more likely than

not, possess the function of a thrombin receptor. As such, it is Applicants' position that the novel protein will find utility in identifying modulators of the thrombin receptor family.

Based on the foregoing, Applicants respectfully submit that the rejections under 35 U.S.C. §101 and 112, first paragraph, for lack of utility, be withdrawn. A notice to that effect is earnestly solicited.

The rejection of claims 2 and 3 under the first paragraph of Section 112, are rendered moot in view of the amendments above. Specifically claim 3 has been canceled and claim 2 has been rewritten and new claims 18 and 19, each encompassing a specific nucleotide sequence. Support for new claim 19 is found at page 5, lines 21 and 22.

II. The Rejection of Claim 3 Under 35 U.S.C. §112, Second Paragraph and 35 U.S.C. §102 As Anticipated by Stratagene (1991) May Properly Be Withdrawn:

The rejection of claim 3 under Section 112, second paragraph and under section 102 as anticipated by Stratagene (1991) is likewise rendered moot in view of the above amendment in that claim 3 has been canceled.

For all the above reasons, Applicant respectfully submit that the claims are allowable over the cited references. In view of the foregoing, the application is now believed to be in proper form for allowance and notice to that effect is earnestly solicited.

If the Examiner believes that a telephone conference would be of value, he is requested to call the undersigned counsel at the number listed below.

Any additional fees required in connection with this submission may be taken from Merck Deposit Account No. 13-2755.

Respectfully submitted,

By _____

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